

## **REMARKS**

### **The Amendment to the Title and Claims**

The title of the application has been amended to define the instantly claimed subject matter. Claims 1-22 and 38 were canceled without prejudice by the amendment filed on November 2, 2005 and April 25, 2007. Applicant reserves the right to prosecute the subject matter of any canceled claims in one or more continuation, continuation-in-part, or divisional applications. Claims 23, 24 and 39 have been amended to define the active ingredient and its dose ranges. The claim is supported by *e.g.*, claim 10 and paragraphs [0122] and [0147] of the specification originally filed. Claims 41-43 have been added for a capsule and dosages. The claims are supported by the originally filed specification, *e.g.*, paragraphs [0122], [0147], [0149], [157], [0158] and [0159]. Claim 44 has been added for the specific types of macular degeneration. The claim is supported by the originally filed specification, *e.g.*, paragraphs [0023] and [0120], and claim 6. No new matter has been added. Claims 23-37 and 39-44 are pending in this application. Applicant respectfully submits that the pending claims are allowable, because the rejection in Office Action is moot in view of the amendment.

### **The Claimed Invention is Not Obvious**

Claims 23-40 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over WO 02/064083 to Treston *et al.* ("Treston") in view of U.S. Patent No. 6,479,512 to Fraley *et al.* ("Fraley"). (Page 2 of the Office Action).

In particular, it is alleged that Treston teaches the uses of S (-) 3-amino-thalidomide, R (+) 3-amino-thalidomide and the dosages for the treatment of macular degeneration, and that it would have been obvious to one skilled in the art to use the compounds for the treatment. Page 3 of the Office Action. Applicant respectfully traverses the rejection.

The U.S. Supreme Court has recently addressed the test for obviousness under 35 U.S.C. § 103. *KSR International Co. v. Teleflex Inc.*, 127 L.Ed.2d 705, 82 U.S.P.Q.2d 1385 (2007). In *KSR*, the Supreme Court rejected the Federal Circuit's *rigid application* of the "teaching, suggestion, motivation" test ("the TSM test") in determining obviousness in the particular case in question. *Id.* at 1395. According to the Supreme Court, the correct analysis is set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). *Id.* However, the *KSR* decision indicated that while the TSM test is not the sole method for determining obviousness, it may still be used and in some cases is helpful. *Id.* at 1396. ("When it first established [the TSM test], the Court...captured a helpful insight."). Indeed, on May 3, 2007,

the Deputy Commissioner of Patents circulated a memorandum to the Technology Center Directors pointing out that the TSM test was not completely abolished in *KSR*. The revised PTO Examiner Guidelines state that examiners can still use the TSM test.

The *Graham* factual inquiries, which establish a guide for determining obviousness, are: (1) determine the scope and contents of the prior art; (2) ascertain the differences between the prior art and the claims at issue; (3) resolve the level of ordinary skill in the pertinent art; and (4) evaluate any evidence of secondary considerations. *KSR*, 82 U.S.P.Q.2d at 1395 (citing *Graham*, 383 U.S. at 15-17); and *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, No. 06-1329, (Fed. Cir., 2007).

The instant claims are not obvious because the references cited by the Examiner differ substantially from the subject matter of the instant claims. Furthermore, the scope and content of the references cited by the Examiner do not provide a reason that would have prompted one of ordinary skill in the art to arrive at the methods of the instant claims.<sup>1</sup>

**1. The methods of the instant claims differ substantially from those of cited art.**

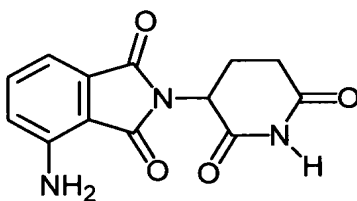
In *KSR*, the Supreme Court noted the significance of the specific facts in question. Indeed, the District Court found that the invention at issue was simply a combination of two known elements from the prior art. *KSR*, 82 U.S.P.Q.2d at 1396. Once these specific findings were made, the Court then determined whether it was obvious to combine the teaching of the prior art to arrive at the claimed invention. *Id.* Thus, the threshold issue to be resolved is the differences between the claims at issue and the prior art.

This case is not a simple combination of two known elements. Instead, the pending claims as amended recite, *inter alia*, methods of treating macular degeneration comprising administering 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione in an amount of from about 5 mg to about 50 mg per day, alone or in combination with a second active agent, as recited in claim 23 or 30. The prior art must teach or suggest each element of the claims to support the PTO's obviousness.

Treston relates to S (-) 3-amino-thalidomide and R (+) 3-amino-thalidomide of the formula:

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<sup>1</sup> Applicant believes that the cited art does not even suggest the combination of the two references, much less a reason that a person in the art would have combined the references.



and their uses and synthesis. These compounds are distinct from the compound recited in the amended claims of the present case. Treston does not disclose or suggest the specific compound, 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, recited in the instant claims, or the use in treating macular degeneration. Treston fails to teach or suggest the the specific compound recited in the claims, less use for treating specific disease macular degeneration as in the claimed methods, or the use of the claimed doses. Thus, from reading Treston, one skilled in the art would not have arrived at the claimed methods of treating patients with macular degeneration with the recited compound in the specific amounts.

Further, Treston does not provide one skilled in the art with any motivation for the claimed methods. Treston is devoid of any motivation to use the specific compound, 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, in specific methods, in the specific doses in a specific patient with macular degeneration. Treston fails to motivate the methods of using the specific amounts of the recited compound for treating a specific disease. In view of the foregoing, substantial differences exist between the instant claims and the cited art, and the instant claims are not obvious over the reference.

**2. The teachings of the references would not prompt a person of ordinary skill to combine the elements to arrive at the methods of the instant claims.**

In *KSR*, the Supreme Court emphasized that the “combination of familiar elements according to known methods is likely to be obvious when it yields no more than predictable results.” *KSR*, 82 U.S.P.Q.2d at 1395. However, the Court cautioned that “[f]ollowing these principles may be more difficult in other cases...because the claimed subject matter may involve more than the simple substitution of one known element for another....” *Id.* at 1396. Further, “it can be important to *identify a reason* that would have prompted a person of ordinary skill...to combine the elements in the way the claimed new invention does.” *Id.* (emphasis added).

It is alleged that Fraley discloses the use of a second active ingredient as angiogenesis inhibitors for the treatment of macular degeneration, and that the combination therapy is obvious to one skilled in the art. Page 3 of the Office Action issued January 26, 2007. Applicant respectfully traverses the rejection.

Pending claims 30-33 recite, *inter alia*, methods of treating macular degeneration comprising a second active agent and from about 5 mg to about 50 mg per day of the specific compound, 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione.

As discussed above, a *prima facie* case of obviousness has not been established for the use of the specific compound, 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione. Thus, the combination therapy using the compound and a second active agent cannot be obvious.

Fraley teaches that angiogenesis inhibitors can be used in combination with the compounds of the tyrosine kinase inhibitors disclosed therein. (Column 10, lines 21-35). First, the specific compound recited in the pending claims, 3-(4-amino-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, is not known to be a tyrosine kinase inhibitor. Second, Fraley is silent as to the specific compound, let alone the specific amounts of from about 5 mg to about 50 mg per day, much less the use of the specific compound in specific amounts for treating macular degeneration, as recited in the present claims. Thus, Fraley suggests nothing about the combination therapy using the recited compound and other agents in treating macular degeneration as claimed. Accordingly, Treston in combination with Fraley does not provide any suggestion or motivation for the claimed methods using the recited compound in specific amounts and a second agent in treating macular degeneration.


As established above, the instant case does not involve a “simple substitution” of known elements in the prior art. Indeed, Treston and Fraley in combination do not have all elements of the claims amended herein. It is only with hindsight that the Examiner contends that the claimed invention is obvious. The Office must provide a reason why one of ordinary skill in the art would combine the teachings of the references cited by the Office, and somehow arrive at the methods of the instant claims. The Office has provided no reason that a person of ordinary skill would have combined the teachings of the references. The Office also must articulate a reason why one of ordinary skill in the art would modify these references to arrive at the methods of the instant claims. *KSR, slip op.* p. 15; *Takeda Chemical Industries Ltd. v. Alphapharm Pty. Ltd.*, No. 06-1329, (Fed. Cir., 2007); and USPTO Memorandum. Because the Office has not met this burden, the instant claims are not obvious over the combination of Treston and Fraley. *Id.* Thus, a *prima facie* case of obviousness has not been established and the rejection must be withdrawn.

**Conclusion**

In view of the foregoing, all the rejections of the claims should be withdrawn. Reconsideration, entry of the above amendment and remarks, and allowance of the pending claims are respectfully requested. Should the Examiner not agree that all claims are allowable, a personal or telephonic interview is respectfully requested to discuss any remaining issues and to accelerate the allowance of the above-identified application.

Respectfully submitted,

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Yeah-Sil Moon (Reg. No. 52,042)

For: Anthony M. Insogna (Reg. No. 35,203)

**JONES DAY**

222 East 41st Street

New York, New York 10017

(212) 326-3939